Review of the Safety and Feasibility of Rapid Infusion of Rituximab

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Rituximab is a chimeric monoclonal antibody that targets the B-cell CD20 antigen and causes rapid and specific B-cell depletion.[1] When added to standard chemotherapy regimens, rituximab improved both progression-free survival and overall survival outcomes in patients with non-Hodgkin's lymphoma (NHL).[2] The addition of rituximab to fludarabine-based chemotherapy regimens has also demonstrated significantly improved response rates and prolonged progression-free survival in patients with either untreated and relapsed or refractory chronic B-cell lymphocytic leukemia (CLL).[3,4]

Biologic and chemotherapy agents are associated with a risk of infusion-related toxicity. The mechanism by which rituximab elicits infusion reactions remains unclear, although the symptoms associated with the reactions are thought to be related to the release of inflammatory cytokines.[5] The most common adverse reactions of rituximab (incidence $\geq$ 25%) observed in patients with NHL include infusion reactions, the majority of which are mild to moderate (grades 1 and 2) in nature.[6,7] The incidence of any-grade infusion reactions was highest during the first infusion (77%) and decreased with each subsequent infusion.[7] These infusion reactions generally have resolved with slowing or interruption of the infusion and with supportive care. The incidence of grade 3 or 4 infusion-related events in patients was reported to be 9% for the first infusion of rituximab in combination with either CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CVP (cyclophosphamide, vincristine, and prednisone) chemotherapy.[8,9] The risk for severe reactions is greater with increased tumor bulk. Grade 3 or 4 adverse events can include urticaria, hypotension, angioedema, hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. The majority of severe reactions occur approximately 30 to 120 minutes after starting the first infusion.[7,8]

Administration of rituximab can result in serious—including fatal—infusion reactions.[7] Deaths within 24 hours of rituximab infusion have occurred, and approximately 80% of fatal infusion reactions occurred in association with the first infusion. This highlights the importance of careful monitoring of patients during infusions, and administration should be discontinued and supportive treatment provided for grade 3 or 4 infusion reactions.[7]

As a consequence of the risk of infusion reactions, a cautious administration schedule has been established, recommending a slow initial infusion rate, followed by increasing the rate in 30-minute increments as tolerated.[7] The result is both a time- and labor-intensive process with an average first infusion time of 6 hours and 4 hours for subsequent infusions.[6] Medicare reimbursement significantly decreases after the first hour of infusion, and longer times place an additional financial burden on infusion centers.[10] Shorter infusion times would yield substantial time savings for patients and benefit outpatient infusion facilities by increasing both the number of infusion chairs available during clinic hours and nursing efficiencies.

The safety and feasibility of two alternate rapid-infusion protocols, a 60-minute and a 90-minute infusion schedule, have been investigated in a number of studies. The 60-minute protocol involved administration of rituximab at either a constant rate or rate escalation after the first 15 minutes for completion of the total dose within 60 minutes.[11-15] The 90-minute protocol was developed with 20% of the rituximab dose administered in the first 30 minutes, with the remaining 80% over the following 60 minutes.[6,16-20]

All of the surveyed studies on both rapid-infusion protocols required standard administration of at least the initial rituximab dose to gauge patient tolerance. Several studies investigated whether administration of steroid premedication was necessary with rapid infusion (Table 1).[14,17] Rituximab was administered in combination with a variety of chemotherapy-containing regimens or as monotherapy in both induction and maintenance settings. The majority of treated patients were diagnosed with NHL or CLL. The reported safety results from studies of both rapid-infusion protocols are summarized in Table 1. Overall, few adverse events were observed, the vast majority of which were grade 1 in nature. The largest study of 206 patients enrolled on the 90-minute protocol, 56 of whom received rituximab as maintenance therapy, reported a single grade 1 event.[6] Follow-up on an additional 1,232 patients has shown that only one patient experienced a significant (grade 3) reaction.[6] In a prospective study of 61 patients enrolled on the 90-minute protocol, no toxicity was reported, and efficacy results demonstrated that complete response and overall survival rates were comparable to those observed with standard infusion in both the phase III Groupe d'Etude des Lymphomes de l'Adulte LNH 98-5 and MabThera (Rituximab) International trials.[8,20,22]

Patients with high numbers of circulating malignant cells or pre-existing cardiac or pulmonary conditions and those who experience significant cardiopulmonary adverse events with the first infusion are at increased risk of an infusion reaction.[5] A study of 42 patients, each receiving an average of 6.5 rapid infusions (60-minute protocol), included 24 patients with at least one cardiovascular risk factor.[23] Although patients with

Table 1. Reported Safety Results From Rapid Infusion of Rituximab

Study	No. of Patients	Premedication	Infusion-Related Adverse Events
60-min Infusion			
Byrd, 2001[11]	33 (26 CLL, 7 SLL)	Diphenhydramine/acetaminophen	No accelerated infusion-related reactions
Aurran-Schleinitz, 2005[12]	69 (56 NHL, 11 CLL)	Diphenhydramine/acetaminophen + steroids	Grade 1 event in 1 patient
Provencio, 2006[13]	40 (39 NHL, 1 Hodgkin's)	Dexchlorpheniramine/paracetamol + steroids	Grade 1 events: chills (2); limited cutaneous reaction with rash (2); fever (1)
Siano, 2008[14]	32 NHL	Clemastine/paracetamol	Grade 1–2 events: headache (4); asthenia (3); dyspnea (1); hypotension (1)
Tuthill, 2009[15]	54 (48 NHL, 1 maltoma, 5 ITP)	Chlorphenamine/paracetamol + hydrocortisone	No grade 3 or 4 adverse events
90-min Infusion			
Middleton, 2005[16]	23 (20 NHL, 2 ITP, 1 dermatomyositis)	Promethazine/paracetamol + hydrocortisone	Grade 1 events: hypothermia (1) Grade 2 events: fevers/rigors requiring infusion interruption (1)
Salar, 2006[17]	70 NHL	Diphenhydramine/acetaminophen	Grade 1 events: sore throat (1); abdominal discomfort (1); fever (1)
Sehn, 2007[6]	206 NHL	Diphenhydramine/acetaminophen + steroids	Grade 1 events in 2 patients
Milone, 2007[18]	31 (27 NHL, 4 CLL)	Diphenhydramine/paracetamol + hydrocortisone	Grade 1 events: abdominal pain (2); hypotension (1); chest pain (1) Grade 3 events: abdominal pain (1)
Corey, 2007[19]	33 NHL	Diphenhydramine/acetaminophen	No adverse events
Gibbs, 2007[20]	61 NHL	Chlorphenamine/paracetamol/tropistetron + prednisolone	No adverse events
Al Zahrani, 2009[21]	21 NHL	Hydroxyzine/acetaminophen	No Grade 3 or 4 adverse events

NOTE. Patients received steroids as part of their premedication regimen where noted. Patients may also have received steroids as part of their treatment protocol (not shown).
Abbreviations: CLL, chronic B-cell lymphocytic leukemia; SLL, small lymphocytic lymphoma; NHL, non-Hodgkin's lymphoma; ITP, autoimmune thrombocytopenia; Hodgkin's, Hodgkins diease.

decreased left ventricular ejection fraction (LVEF) greater than 15% did not recover to baseline LVEF function, none of these patients developed clinical congestive heart failure. A second study of cardiac function in 32 patients (60-minute protocol) reported no clinical alterations by ECG, and only one patient displayed an asymptomatic change.[14] The initial mean LVEF (65.5%; standard deviation, 5.4%) remained unchanged 1 month after the end of treatment.[14] These studies indicate that patients with known cardiovascular risk factors should have cardiac function assessed before treatment and be carefully monitored during and after treatment. The prescribing information for rituximab recommends the careful monitoring of patients with pre-existing cardiac or pulmonary conditions or who have experienced prior cardiopulmonary reactions.[7]

Several large studies are underway to evaluate the safety of the 90-minute infusion protocol. In an open label phase IIIB trial—the MAXIMA (Maintenance Rituximab in Follicular Lymphoma) study—549 patients with follicular lymphoma will receive maintenance rituximab every 8 weeks for a maximum of 2 years at either the standard or 90-minute infusion rate.[24] To date, results have shown that adverse events occurred in 0.9% of rapid infusions (12 of 1,367) compared with 0.8% of standard infusions (32 of 3,980), and no serious adverse events were reported within 24 hours of completion of rapid infusion.[24] The median infusion time was 3.26 hours for the standard administration arm and 1.63 hours for the rapid infusion arm. A phase III, open-label trial—the RATE (Rituximab Alternative Dosing Rate in Patients With Previously Untreated Diffuse Large B-Cell or Follicular Non-Hodgkin's Lymphoma) study—is specifically designed to investigate the safety of the 90-minute infusion protocol and will enroll 385 patients with previously untreated diffuse large B-cell or follicular non-Hodgkin's lymphoma.[25] The primary end point for this study is to evaluate the frequency of grade 3 or 4 infusion-related toxicity.

The studies reported here were conducted in a number of countries, including Switzerland, France, Argentina, Canada, Spain, the United Kingdom, and Saudi Arabia, in addition to the United States and indicate that rapid infusion is being used internationally to administer rituximab.[6,12-15,17-20] A survey of 20 cancer centers in the United Kingdom reported that 70% use the 90-minute protocol and 5% use the 60-minute protocol, with the remainder using standard administration.[15] The extent of rapid-infusion usage in the United States is unknown at this time. Currently, rapid-infusion protocols are not utilized in the Department of Lymphoma and Myeloma at M. D. Anderson Cancer Center as we await data from the ongoing large RATE trial to definitively ascertain the safety of rapid infusion. We are fortunate that time and resource constraints are not an issue at our institution.

Overall, the results of studies to date suggest that after the first dose of rituximab has been given in a standard manner, subsequent doses can be safely administered by rapid-infusion protocols.

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Author's Disclosures of Potential Conflicts of Interest
The author indicated no potential conflicts of interest.

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